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09/076,404	05/12/1998	DAVID J. ECKER	IBIS-0007US	4802
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Pepper Hamilton LLP 400 Berwyn Park 899 Cassatt Road Berwyn, PA 19312-1183			EXAMINER BRUSCA, JOHN S	
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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/076,404
Filing Date: May 12, 1998
Appellant(s): ECKER ET AL.

Paul K. Legaard
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 30 July 2009 appealing from the Office action
mailed 17 November 2008

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

The rejection of claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn because after further consideration the limitation of using a human target RNA that

comprises a molecular interaction site of less than 30 nucleotides, present in all independent claims, has literal support in the present specification and is adequately shown in the prior art. The claimed subject matter does not limit the type of molecule that interacts with the interaction site. A human target RNA with a 26 nucleotide interaction site is shown in Hentze et al. as cited below. The limitation would be met by human tRNA anticodon interaction sites, a human RNA targeted by an interfering RNA molecule, and a human RNA that is a substrate of a ribonuclease. The limitation is also met by any human RNA sequence of less than 30 nucleotides because any RNA sequence can bind a polynucleotide with a complementary sequence of nucleotides.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,337,183

Arenas et al.

1-2002

Murray et al. "PRO_SELECT: Combining structure-based drug design and combinatorial chemistry for rapid lead discovery. 1. Technology" Journal of Computer-Aided Molecular Design, vol. 11 (1997), pp. 193-207

Sezerman et al. "Toward computational determination of peptide-receptor structure" Protein Science, vol. 2 (1993), pp. 1827-1843

Greig et al. "Measurement of Macromolecular Binding Using Electrospray Mass Spectrometry. Determination of Dissociation Constants for Oligonucleotide-Serum Albumin Complexes" Journal of the American Chemical Society, vol. 117, (1995), pp. 10765-10766

Hentze et al. "Identification of the Iron-Responsive Element for the Translational Regulation of Human Ferritin mRNA" Science, vol. 238, (11 December 1987), pp. 1570-1573

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al. in view of Arenas et al. in view of Sezerman et al. in view of Greig et al. in view of Hentze et al.

The claims are drawn to a method of using an in silico, i.e. computer based, virtual library of compound structure data to identify a structure that binds a human target RNA with an interaction site of less than 30 nucleotides. The compounds are synthesized and analyzed by generation of ionized fragments (exemplified in the specification by use of mass spectroscopy) of the RNA complexed with the compound. In some embodiments the identified compounds are ranked for binding strength, the target RNA is compared to RNA of different taxonomic species, and the target has a stem, hairpin, or loop structure that is within an untranslated region.

Murray et al. shows a method of designing and use of in silico virtual libraries of compounds to select structures that have a desired binding specificity in the abstract and throughout. Murray et al. shows ranking of members of the library on pages 203-204 for predicted binding strength. Murray et al. shows the general applicability of their method throughout and shows an example of thrombin inhibitors, and their subsequent synthesis and testing on page 204. Murray et al. provides guidance in the abstract and in the second column of page 194 to first screen potential interacting molecules in silico and to subsequently synthesize and test selected compounds experimentally for interaction.

Murray et al. does not show RNA binding compounds.

Arenas et al. shows an experimental, i.e. not in silico, screening method for compounds that bind RNA in the abstract and throughout. Arenas et al. shows that the compounds may be selected from peptides or small organic molecules in column 5, lines 62-67, and antibiotics in column 1, lines 56-59. Arenas et al. shows in column 1 that small molecules can be used to block functions of the target RNA. Arenas et al. shows in column 6, lines 40-41 that the target RNA may be from any living organism.

Sezerman et al. shows in the abstract and throughout methods of using in silico virtual peptide structures to measure binding affinity to a binding target.

Greig et al. shows use of electrospray mass spectroscopy of peptide-oligonucleotide complexes to measure binding strength, with results shown in figure 2.

Hentze et al. shows a human iron responsive element (IRE) in the 5' untranslated portion of ferritin H chain messenger RNA (mRNA). Hentze et al. uses a progressive deletional analysis to determine the location and size of the IRE, see pages 1570-1571. Hentze et al. shows in figure 1, and Table 1 that the element confers responsiveness to media iron content to increase translation of the mRNA. Hentze et al. shows in the third column of page 1571 and figure 2 that computer modeling of the IRE predicts a stem-and-loop structure. Hentze et al. show in Figures 2 and 3 construction and assay of a 26 base synthetic oligonucleotide fragment of the IRE. Hentze et al. compares the human sequence to orthologous sequences from other species in figure 2 and the discussion on page 1572 and concludes that the sequence is highly conserved during evolution. Hentze et al. shows in Figure 3 that the fragment of the IRE is sufficient to confer iron responsiveness of translation to a human growth hormone reporter gene. Hentze et al.

provides guidance in the third column of page 1572 to use the IRE to produce regulatable expression vectors.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the *in silico* screening method of Murray et al. by use of the RNA targets of Arenas et al. because Arenas et al. shows bioassays that screen for compounds that bind to RNA targets, and because Murray et al. provides guidance to confirm the *in silico* results with experimental assays using the molecules selected by the *in silico* method. It would have been further obvious to use mass spectroscopy to analyze binding strength because Sezerman shows that peptides may be analyzed *in silico* for binding, and Greig et al. shows that mass spectroscopy may be used to determine the binding affinity of a complex of a peptide and an oligonucleotide, and experimental determination of binding strength is an important parameter for determination of biological activity. It would have been further obvious to use the IRE target sequence of Hentze et al. because Hentze et al. shows that the human IRE RNA target sequence has a role in cell iron metabolism, and because Hentze et al. provides guidance that the IRE can be used to produce a regulatable expression vector. Development of compounds that bind to the human IRE would allow for development of compounds that inhibit or enhance expression of wild type or recombinant genes in human cells as suggested by Arenas to allow for insights into the function of naturally occurring mRNA, or to regulate gene expression of recombinant genes comprising the IRE.

(10) Response to Argument

The Appellants state that the applied references do not show the limitation of claim 26 regarding identifying a molecular interaction site by comparison of a target RNA to nucleotide

sequences of different taxonomic species; however Hentze et al. shows that comparison as specifically noted in the rejection above. The comparison to other taxonomic species identified a conserved domain, which is in agreement with the mapping of the domain by progressive deletional analysis. The Appellants state that there is no motivation to contact the target RNA with a binding compound and to further study the resulting complex by mass spectrometry. However such motivation is discussed in the rejection above, particularly with regard to the Greig et al. reference. The Appellants state that the Murray et al. reference shows in silico analysis which is incompatible with the mass spectrometry analysis of Greig et al., however the in silico and experimental approaches of these two references are not in conflict, the two references show complementary methods of studying formation of binding complexes, each with advantages such as speed and ability to assay a large range of potential compounds for the in silico method, and accuracy and experimental confirmation of predicted complex formation for the mass spectrometry method. It is further noted that Murray et al. provides explicit guidance in the introduction on page 194 and the example on page 204 to perform experimental testing of binding by using the molecules identified in the in silico method of Murray et al.

11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/John S. Brusca/

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